CTLA4 Blockade in Melanoma Treatment

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University of California Los Angeles.
CTLA4 Negatively Modulates T-Cell Activation
Blocking Antibodies to CTLA4 Allow Positive Signaling from Costimulatory Molecules to T Cells

### CTLA4 Antagonistic Monoclonal Antibodies in Clinical Development

<table>
<thead>
<tr>
<th>Antibody Name</th>
<th>Former Name</th>
<th>Maker</th>
<th>Type of Antibody*</th>
<th>Ig Subtype*</th>
<th>Plasma Half Life*</th>
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</thead>
<tbody>
<tr>
<td>ipilimumab</td>
<td>MDX010</td>
<td>Medarex</td>
<td>Fully human</td>
<td>IgG1</td>
<td>15 days</td>
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<tr>
<td></td>
<td>BMS734016</td>
<td>BMS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>tremelimumab</td>
<td>CP-675,206</td>
<td>Pfizer</td>
<td>Fully human</td>
<td>IgG2</td>
<td>22 days</td>
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<tr>
<td></td>
<td>ticilimumab</td>
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<table>
<thead>
<tr>
<th></th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
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<tbody>
<tr>
<td>ADCC</td>
<td>+++</td>
<td>+/-</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Complement fixation</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
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<tr>
<td>Plasma Half Life</td>
<td>23</td>
<td>23</td>
<td>9</td>
<td>23</td>
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</tbody>
</table>

Ribas et al. J Clin Oncol 2005
## Published Full Text Manuscripts of Antitumor Activity of Anti-CTLA4 mAb in Melanoma

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Antibody</th>
<th>Combination</th>
<th>mAb Dose</th>
<th>Ab. Dose</th>
<th>No. Pts with Measurable Melanoma</th>
<th>Objective Responses</th>
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<tbody>
<tr>
<td>Hodi <em>et al.</em> PNAS 03</td>
<td>Ipilimumab (MDX010)</td>
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<td>3 mg/kg</td>
<td>Single</td>
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<td>0</td>
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<tr>
<td>Attia <em>et al.</em> JCO 05 (Phan <em>et al.</em> PNAS 03)</td>
<td>Ipilimumab (MDX010)</td>
<td>gp100 peptides</td>
<td>3 mg/kg</td>
<td>q3w</td>
<td>56</td>
<td>7</td>
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<td>Maker <em>et al.</em> Ann Surg Onc 05</td>
<td>Ipilimumab (MDX010)</td>
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<td>q3w</td>
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<tr>
<td>Maker <em>et al.</em> J Immunotheron 06</td>
<td>Ipilimumab (MDX010)</td>
<td>No</td>
<td>3-9 mg/kg</td>
<td>q3w</td>
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<td>5</td>
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<tr>
<td>Ribas <em>et al.</em> JCO 05</td>
<td>Tremelimumab (CP-675,206)</td>
<td>No</td>
<td>0.01-15 mg/kg</td>
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<td>Tremelimumab (CP-675,206)</td>
<td>No</td>
<td>10-15 mg/kg</td>
<td>q1m or q3m</td>
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<td>5</td>
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</tbody>
</table>

Overall: 10-15% RR
Early Clinical Development Issues

- What is the maximum tolerable dose?
- What are the optimal plasma levels?
- What is the right dose?
- What is the right schedule?
- What is the mechanism of action of response and resistance?
- Are there biomarkers for response?
## Phase 1: Toxicity and Response with CP-675,206

<table>
<thead>
<tr>
<th>Dose Level (mg/kg)</th>
<th>No. Patients Evaluable for Response</th>
<th>Response (months)</th>
<th>Autoimmune Toxicities</th>
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<tbody>
<tr>
<td>0.01</td>
<td>3</td>
<td>SD x 16</td>
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</tr>
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<td>3</td>
<td></td>
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<td>1.0</td>
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<td>SD x 12</td>
<td>Vitiligo</td>
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<tr>
<td>3.0</td>
<td>7</td>
<td>SD x 15</td>
<td>Diarrhea, Lipase</td>
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<tr>
<td></td>
<td></td>
<td>CR x 62+</td>
<td>Vitiligo, Asthma</td>
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<tr>
<td>6.0</td>
<td>4</td>
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<tr>
<td>10.0</td>
<td>9</td>
<td>SD x 7</td>
<td>Diarrhea, Rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PR x 53+</td>
<td>Panhypopituitarism</td>
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<tr>
<td></td>
<td></td>
<td>SD x 11</td>
<td>Hyperthyroidism</td>
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<tr>
<td>15.0</td>
<td>6</td>
<td>PR x 50+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CR x 50+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CR x 51+ (removal of 1 lesion)</td>
<td></td>
</tr>
</tbody>
</table>

Increasing the dose leads to responses and toxicities

Ribas, Camacho, Gomez-Navarro et al. JCO 2005, Update 07/07
Antibody Exposure/PD Correlation

- Preclinical testing:
  - Concentration-dependent IL-2 release in PBMC
  - Predicted minimal efficacious plasma concentration: 10-30 µg/ml

- Clinical testing:
  - PD effects (toxicity and/or response): Doses leading to sustained plasma levels beyond 30 µg/ml

In vitro

In vivo

D. Hanson

D. Noe
Anti-CTLA4 Brief Clinical Summary

• A threshold of circulating antibody is required for biological effects, which result in:
  – No toxicity and no response in the majority of patients.
  – Toxicity and/or response in a minority of patients (10-25%).

• Responses are durable, longest 6 years, with very few relapses.

• The key issue is to understand the MOA of response and toxicity.
Immune Monitoring in Peripheral Blood

• After analyzing 3,094 data points of samples obtained from peripheral blood:
  – MHC Tetramers (719).
  – ELISPOT (1,694).
  – Flow cytometry for T cell activation marker HLA-DR and T cell memory marker CD45RO on CD4 and CD8 cells (606).
  – FoxP3 by QPCR (56) and ICS (19).

• Conclusion: Non-specific markers of activation of CD4+ T cells are the only biomarker of CP-675,206 administration, which provides little mechanistic insight.
Partial Response (31+ mo)

02/05

03/05

07/05

Post

Negative Stain

HMB45 Melanoma

CD20 B Cells

CD3 T Cells

CD4 T helper

CD8 CTL
Partial Response (31+ mo)

Peripheral blood

Tumor biopsy

- gp100 Tetramer
- CD8+

- H&E
- MART-1
- CD20
- CD8
- CD4
- CD1a

- 10x
- 40x
Study of Intratumoral Changes after CP-675,206

• 89 patients dosed with CP-675,206 at UCLA, a small subset of patients underwent tumor biopsies

• Samples collected for:
  – Diagnostic or therapeutic need (more likely on progressing patients)
  – Research purposes under UCLA IRB# 02-08-067 (more likely on responding patients)

• IHC staining for:
  – Melanoma markers: S-100, HMB45, MART-1, tyrosinase
  – Immune cell subset markers: CD1a, CD3, CD4, CD8, CD20
  – Treg marker: FoxP3
  – Immune suppressive DC marker: IDO

• IHC scoring by Dr. Alistair Cochran:
  – Frequency (0-3+) of reactive cells
  – Distribution (diffuse or patchy) of reactive cells
Partial Response (20+ mo)

Phenotype CD8+: HLA-DR+CD45RO+++CD27++CCR7- (T early memory)

<table>
<thead>
<tr>
<th>Color</th>
<th>Marker</th>
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<tbody>
<tr>
<td>AlexaFluor405/PacificBlue</td>
<td>CD3</td>
</tr>
<tr>
<td>FITC</td>
<td>CD45RO</td>
</tr>
<tr>
<td>PE</td>
<td>CD27</td>
</tr>
<tr>
<td>PC5/7AAD (Dump Channel)</td>
<td>CD19/CD56</td>
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<tr>
<td>ECD</td>
<td>HLA-DR</td>
</tr>
<tr>
<td>APC/AlexaFluor647</td>
<td>CCR7</td>
</tr>
<tr>
<td>APC-Cy7/APC-AF750</td>
<td>CD4</td>
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</table>

CD8+: 41%, CD4+: 6.5%
Intratumoral CD8 and CD4 T Cell Infiltrates

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Response</th>
<th>Timing of Biopsy (first dose/last dose)</th>
<th>CD8</th>
<th>CD4</th>
<th>Change</th>
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<tbody>
<tr>
<td>1</td>
<td>PR</td>
<td>Pre</td>
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<td>NA</td>
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<td></td>
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<td>Post (3 mo/3 mo)</td>
<td>+++ diffuse</td>
<td>++ diffuse</td>
<td>↑</td>
</tr>
<tr>
<td>2</td>
<td>PR</td>
<td>Pre</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post (2 mo/1 mo)</td>
<td>++ diffuse</td>
<td>+ diffuse</td>
<td>↑</td>
</tr>
<tr>
<td>3</td>
<td>pPR</td>
<td>Pre</td>
<td>++ patchy</td>
<td>+ patchy</td>
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<tr>
<td></td>
<td></td>
<td>Post (9 mo/1 mo)</td>
<td>++ diffuse</td>
<td>+++ diffuse</td>
<td>↑</td>
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<tr>
<td>4</td>
<td>Progression</td>
<td>Pre</td>
<td>+/- patchy</td>
<td>+/- patchy</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Post (1 mo/1 mo)</td>
<td>+/- patchy</td>
<td>+/- patchy</td>
<td>=</td>
</tr>
</tbody>
</table>
Treg Depletion with CTLA4 Blocking Monoclonal Antibodies

- Treg depletion in peripheral blood with anti-CTLA4 mAb:
  - Reuben *et al.* Cancer 2006

- No Treg depletion in peripheral blood with anti-CTLA4 mAb:
  - Maker *et al.* J Immunol 2005
  - Comin-Anduix *et al.* iSBTc 2006
Patient PD: FoxP3 by IHC or ICS in TIL

FoxP3 in TIL by IHC

FoxP3 in TIL by ICS

CD4

CD25

0.47% CD4=CD25high

CD4+/CD25hi

92%

FoxP3 ICS

FoxP3 in TIL by ICS

CD4/CD25hi

FoxP3 IHC

FoxP3 in TIL by IHC

CD4

CD25

0.47% CD4=CD25high

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92%

FoxP3 ICS

FoxP3 in TIL by ICS

CD4/CD25hi

FoxP3 IHC

FoxP3 in TIL by IHC

CD4

CD25

0.47% CD4=CD25high

CD4+/CD25hi

92%

FoxP3 ICS

FoxP3 in TIL by ICS
pPR: FoxP3 Pre and Post CP-675,206

Pre

HMB45

CD8

Post

HMB45

CD8

4x

10x

40x
Inhibition of IDO by CTLA4 Blocking Monoclonal Antibodies

pPR: IDO Pre and Post CP-675,206

Pre

HMB45

CD8

Post

HMB45

CD8

4x 10x 40x
# Intratumoral FoxP3+ and IDO+ Cells

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Response</th>
<th>Timing of Biopsy</th>
<th>FoxP3</th>
<th>FoxP3 Change</th>
<th>IDO</th>
<th>IDO Change</th>
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<tbody>
<tr>
<td>1</td>
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<td>Pre</td>
<td>0</td>
<td>↑</td>
<td>++ diffuse</td>
<td>↓</td>
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<td></td>
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<td>Post (3 mo/3mo)</td>
<td>+ patchy</td>
<td>+ patchy</td>
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</tr>
<tr>
<td>2</td>
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<td>Pre</td>
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<td>↑</td>
<td>+ patchy</td>
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<td></td>
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<td>Post (2 mo/1 mo)</td>
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<td>3</td>
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<td>=</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post (9 mo/1 mo)</td>
<td>++ patchy</td>
<td>+ patchy</td>
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<tr>
<td>4</td>
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<td>Pre</td>
<td>+ patchy</td>
<td>=</td>
<td>-</td>
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<td></td>
<td></td>
<td>Post (1 mo/1 mo)</td>
<td>+ patchy</td>
<td>=</td>
<td>-</td>
<td>=</td>
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</table>
CTLA4 mAb Clinical Development Leading to Pivotal Clinical Trials

**Early Clinical Data**

**MDX010**

FIH 3 mg/kg 06/2000
- 10 mg/kg q3w 23 pts RR: 8% G3/4:10% (?)
  - + gp100 pep 3 mg/kg q3w 56 pts RR: 12.5% G3/4: 25%
  - + DTIC 3 mg/kg q4w 35 pts RR: 17% G3/4: 28.6%
  - 3 mg/kg q4w 37 pts RR: 5% G3/4: 18.5%

**CP-675,206**

FIH 0.01-15 mg/kg 01/2002
- 15 mg/kg q12w 44 pts RR: 7% G3/4: 13%
- 10 mg/kg q4w 44 pts RR: 10% G3/4: 27%

**Pivotal Trials**

- Single arm in 2nd line:
  1. Ipi 10 mg/kg q3w

- Randomized in 2nd line:
  1. gp100 pep
  2. Ipi 3 mg/kg q3w
  3. Ipi 3 mg/kg q3w + gp100

- Randomized in 1st line:
  1. DTIC
  2. Ipi 10 mg/kg q3w + DTIC

- Single arm in 2nd line:
  1. Treme 15 mg/kg q12w

- Randomized in 1st line:
  1. DTIC
  2. Treme 15 mg/kg q12w

(1) Weber, J et al. Proc ASCO 07
(2) Attia, P et al. JCO 05
(3) Fischkoff, SA et al. Proc ASCO 05, all 95% CI overlapping
(4) Ribas, A et al. Proc ASCO 07, all 95% CI overlapping
Is Dose Correlated with Response or Toxicity or Both?

Anti-Self

Anti-Melanoma

Toxicity

Response
## Is Toxicity Correlated with Response?

- Attia, Rosenberg *et al.* JCO 2005: (ipilimumab + gp100 peptides)

<table>
<thead>
<tr>
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<th>Grade 0-II</th>
<th>Grade III/IV</th>
<th>Total</th>
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<td>42</td>
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<td>56</td>
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</table>

P = 0.008 Fisher exact test
P = 0.002 Chi-square

- Reuben, Camacho *et al.* Cancer 2006: (CP-675,206)

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P = 0.045 Chi-square
Is Toxicity Correlated with Response?

- Attia, Rosenberg *et al.* JCO 2005: (ipilimumab + gp100 peptides)

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  \[P = 0.045 \text{ Chi-square}\]

But…

- Toxicity with no response (red) is more common than toxicity with response (green).
Is Toxicity Correlated with Response?

• Attia, Rosenberg et al. JCO 2005: (ipilimumab + gp100 peptides)

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<td>30</td>
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P = 0.045 Chi-square

But…

• Response without toxicity is possible.
• More doses, more likely to develop toxicities, more likely to demonstrate a response.
### Is Toxicity Correlated with Response?

- **Attia, Rosenberg et al. JCO 2005:** (ipilimumab + gp100 peptides)

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- **Reuben, Camacho et al. Cancer 2006:** (CP-675,206)

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P = 0.045 Chi-square

- **Maker, Rosenberg et al. JIT 2006:** (ipilimumab intra-patient dose escalation)

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<tr>
<td></td>
<td>30</td>
<td>16</td>
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</tbody>
</table>

P = 0.32 Fisher exact test
What Have We Learned Thus Far?

• Responses:
  – Somewhere between 5-15%
  – Most are durable, lasting years.

• Toxicity:
  – Serious autoimmune or inflammatory toxicity in 10-30%.

• Relationship between toxicity and response:
  – Unclear.

• Biomarkers of antitumor activity:
  – Peripheral blood: No good evidence.
  – Tumors: Marked immune infiltrates in responders.

• Mechanism of action:
  – Immune-mediated.
  – Unlikely participation of Treg or IDO+ cells.
# Phase II Registrational Clinical Trials

<table>
<thead>
<tr>
<th>mAb</th>
<th>Population</th>
<th>No. Pts</th>
<th>Primary Objective</th>
<th>Dosing</th>
<th>Init.</th>
<th>Compl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treme-limumab</td>
<td>2nd line or greater</td>
<td>215</td>
<td>Best ORR</td>
<td>15 mg/kg q3m</td>
<td>Dec 05</td>
<td>Oct 06</td>
</tr>
<tr>
<td>Ipi-limumab</td>
<td>2nd line or greater</td>
<td>150</td>
<td>Best ORR</td>
<td>10 mg/kg q3w</td>
<td>Feb 06</td>
<td>Jan 07</td>
</tr>
<tr>
<td>Ipi-limumab</td>
<td>2nd line</td>
<td>210</td>
<td>Best ORR</td>
<td>0.3 mg/kg q3w 3 mg/kg q3w 10 mg/kg q3w</td>
<td>Feb 06</td>
<td>April 07</td>
</tr>
</tbody>
</table>

Source: ClinicalTrials.gov.
# Phase III Registrational Clinical Trials

<table>
<thead>
<tr>
<th>mAb</th>
<th>Treatments</th>
<th>Pop.</th>
<th>No. Pts</th>
<th>Primary Objective</th>
<th>Dosing</th>
<th>Init.</th>
<th>Compl.</th>
</tr>
</thead>
</table>
| Ipi-limumab     | 1. Ipi  
2. gp100  
3. Ipi + gp100 | 2nd line | 750     | Best ORR | 3 mg/kg q3w       | Sept 04 | Ongoing    |
| Treme-limumab   | 1. DTIC or TMZ  
2. Treme     | 1st line | 630     | OS      | 15 mg/kg q3m      | March 06 | June 07    |
| Ipi-limumab     | 1. DTIC  
2. Ipi + DTIC | 1st line | 500     | PFS     | 10 mg/kg q3w      | June 06  | Ongoing    |

Source: ClinicalTrials.gov.
Key Features of the Pivotal Testing

- **Ipilimumab:**
  - Testing single agent, combination with peptides and combination with chemotherapy
  - Testing 3 different dosing regimens
  - Dosing beyond the MTD (more toxicity, more responses?)
  - Phase III: PFS

- **Tremelimumab:**
  - Single agent testing
  - Dosing regimen optimized to minimize toxicity
  - Phase III: OS
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